## REMARKS

Independent claims 18, 36, 41, and 45 have amended so as to add the following limitations:

> a template comprising an unknown nucleic acid molecule
>
> ...
>
> wherein the first and second channels are distinct and separate from the reaction chamber and positioned before and after the reaction chamber;
>
> ...
>
> e) a second Raman detection unit operably coupled to the outlet channel at a location outside the reaction chamber and configured to perform surface enhanced Raman spectroscopy (SERS),
>
> wherein the second Raman detection unit is configured to measure the concentrations of nucleotides by Raman spectroscopy at a location outside the reaction chamber as the nucleotides flow through the outlet channel;

These limitations are supported by the specification as follows:

(1) Paragraph [0036] explains that "the sequence of the template strand 13 can be determined from the sequence of the nascent strand 16." By reading the above sentence, persons skilled in the art would recognize that the template strand 13 has a unknown nucleic acid molecule.

(2) Paragraph [0038] states that "the reaction chamber 11 can be attached to a flow-through system" and that nucleotides "17 can enter the reaction chamber 11 and be incorporated into a nascent strand 16" and the "unincorporated nucleotides 17 can pass out the reaction chamber 11 into a second channel, where they are detection by Raman spectroscopy. ... In such alternatives, duplicate detection units 12 can be positioned before and after the reaction chamber 11." By reading the above statements, persons skilled in the art would recognize that the first and second channels are distinct and separate from the reaction chamber and positioned before and after the reaction chamber; a second Raman detection unit operably coupled to the outlet channel at a location outside the reaction chamber and configured to perform surface enhanced Raman

spectroscopy (SERS), and that the second Raman detection unit is configured to measure the concentrations of nucleotides by Raman spectroscopy at a location outside the reaction chamber as the nucleotides flow through the outlet channel.

**Claim Rejection - 35 U.S.C. §112**

Claims 23 and 40 were rejected under 35 USC 112, first paragraph. This rejection is respectfully traversed.

The Examiner states that "while paragraph 10 supports a mesh in the outlet channel, the specification does not provide support for a mesh in the inlet channel." Thus, claims 23 and 40 have been amended to recite a mesh in the outlet channel."

Claim 23, 40, 42 and 46-47 were rejected under 35 USC 112, second paragraph. This rejection is respectfully traversed.

The phrase "mesh SERS active metal nanoparticles" in claims 23 and 40 was due to an inadvertent error. This phrase has been corrected to "mesh" as in original claim 23.

Claims 42 and 46 were deemed to be indefinite due to the recitation "each Raman detection unit." The Examiner states that independent claims 41 and 45 each have only one Raman detection unit as these claims recite "a Raman detection unit," whereas the phrase "each Raman detection unit" indicates more than one Raman detection units. Applicants respectfully submit that the Examiner's reading of claims 41 and 45 is incorrect that claims 41 and 45 limit the scope of these claims to only one Raman detection unit. The term "a" in a claim means "one or more." The Court of Appeals of the Federal Circuit has stated, "This court has repeatedly emphasized that an indefinite article 'a' or 'an' in patent parlance carries the meaning of 'one or more' in open-ended claims containing the transitional phrase 'comprising.' Unless the claim is specific as to the number of elements, the article 'a' receives a singular interpretation only in rare circumstances when the patentee evinces a clear intent to so limit the article." *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (Fed. Cir. 2000) (citations omitted). Thus, there was nothing wrong with the recitation

of "each Raman detection unit" in claims 42 and 46 when claims 41 and 45 recite "a Raman detection unit." In any case, claims 42 and 46 have been amended to recite "the Raman detection unit." The terms "a Raman detection unit" and "the Raman detection unit" in the claims still carry the meaning of "one or more Raman detection units."

Claims 47 has been amended to recite "the concentrations of nucleotides is measured by Raman spectroscopy as the nucleotides flow through the outlet channel" as suggested by the Examiner.

**Claim Rejection - 35 U.S.C. §103**

Claims 18-23 and 36-52 were rejected as being obvious over Shipwash in view Natan. This rejection is respectfully traversed.

The Examiner states that "Shipwash teaches a reaction chamber containing a single template nucleic acid molecule attached to an immobilization surface; namely, a mixing channel, which is a reaction chamber, further comprising a bead having nucleic acids immobilized thereon (Figures 11 and 14, and paragraph 0066 and 0255)." See page 5, lines 14-16 of the Action. Shipwash is directed to the recognition of amino acids and proteins, "wherein the aminoacyl-tRNA synthetase system is used to analyze amino acids" (see Abstract of Shipwash), *not to the detection of nucleic acid*. Shipwash uses aminoacyl-tRNA, i.e., a nucleic acid molecule, as a probe (*not a template*) to analyze amino acids. The unknown molecules that are analyzed by Shipwash are amino acids and proteins while aminoacyl-tRNA, i.e., a nucleic acid molecule, that is used as a probe has a *known* sequence. On the other hand, in the present invention, the "template comprises an *unknown* nucleic acid molecule" as recited in the independent claims. In short, Shipwash does not disclose "a reaction chamber containing *a template comprising an unknown nucleic acid molecule* attached to an immobilization surface" as recited in the independent claims, and Natan does not fill this gap in Shipwash.

The Examiner acknowledges that in Shipwash "the outlet channel is one end of one of the reaction channels." See page 5, lines 4-5 from the bottom of the Action. On the other hand, independent claims now recite "wherein the first and second channels are distinct and separate from the reaction chamber and positioned *before and after the reaction chamber*." [Emphasis added.] Applicants respectfully submit that Shipwash fails to disclose "wherein the first and second channels are distinct and separate from the reaction chamber and positioned *before and after the reaction chamber*," and Natan fails to fill this gap in Shipwash.

The Examiner further acknowledges that in Shipwash "a second detector is coupled to the outlet (i.e., reaction) channels." See page 6, lines 2-3 of the Action. On the other hand, the independent claims recite "a second Raman detection unit operably coupled to the outlet channel at a location *outside the reaction chamber* and configured to perform surface enhanced Raman spectroscopy (SERS), wherein the second Raman detection unit is configured to measure the concentrations of nucleotides by Raman spectroscopy at a location *outside the reaction chamber* as the nucleotides flow through the outlet channel." [Emphasis added.] In short, Shipwash fails to disclose "a second Raman detection unit operably coupled to the outlet channel at a location *outside the reaction chamber* and configured to perform surface enhanced Raman spectroscopy (SERS), wherein the second Raman detection unit is configured to measure the concentrations of nucleotides by Raman spectroscopy at a location *outside the reaction chamber* as the nucleotides flow through the outlet channel," and Natan fails to fill this gap in Shipwash.

Claims 49-52 have been rejected as being obvious over Shipwash in view of Natan, further in view of French. This rejection is respectfully traversed.

As explained above, Shipwash is directed to the recognition of amino acids and proteins, "wherein the aminoacyl-tRNA synthetase system is used to analyze amino acids" (see Abstract of Shipwash), *not to the detection of nucleic acid*. Shipwash uses aminoacyl-tRNA, i.e., a nucleic acid molecule, as a probe (*not a template*) to analyze amino acids. On the other hand, French is related to detecting nucleic acids. The Examiner states that "[i]t would ... have been obvious to a person of ordinary skill in the art at the time of the claimed invention to have modified the apparatus of

Shipwash in view of Natan with the confined reagents [i.e., the template, the primer and the polymerase confined to the reaction chamber] as taught by French et al with a reasonable expectation of success." See page 18, lines 1-3 from the bottom of the Action. Applicants respectfully submit that the Examiner's above-mentioned position is incorrect as explained below.

Persons of ordinary skill in the art would recognize that one needs to use the primer and the polymerase in a reaction chamber *only* when the apparatus is used for detecting the sequence of a nucleic acid molecule as in the case of French. On the other hand, one does *not* need to use the primer and the polymerase in a reaction chamber when the apparatus is used for recognizing amino acids and proteins as in the case of Shipwash. Thus, persons of ordinary skill in the art would have had no reason or expectation of success whatsoever at the time of the present invention to modify the apparatus of Shipwash with the confined reagents of French, i.e., "wherein the template, the primer and the polymerase are confined in the reaction chamber" as recited in claims 49-52, in light of the teaching of French.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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